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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/853,731 | 05/11/2001 | Apollon Papadimitriou | 20619 | 6504 |

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| EXAMINER | |
|---|---|
| KAM, CHIH MIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1656 | |

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/853,731 | PAPADIMITRIOU, APOLLON | |
| | Examiner | Art Unit | |
| | Chih-Min Kam | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,25,27-34,38-42,51-55,59-61,67,68,71-77 and 83-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *24,25,27-34,38-42,51-55,59 and 90* is/are allowed.

6)☒ Claim(s) *60,61,67,68,71-77,83-89 and 91-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/25/06;2/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Claims*

1. Claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 are pending.

Applicants' amendment filed on January 23, 2006 is acknowledged. Applicants' response has been fully considered. Claims 83 and 88 have been amended. Thus, claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 are examined.

### *Priority*

2. The instant application claims the priority of EP 00110355.5, filed May 15, 2000. However, the EP document does not disclose methionine as an antioxidant for the claimed composition, thus, the priority date of the claimed composition comprising methionine is the effective filing date of parent application, May 11, 2001.

### *Information Disclosure Statement*

3. Applicants' IDS filed January 25 and February 16 are acknowledged. Most of the references listed on the IDS and the Opposition filed by Sandoz against European Patent EP1311285 (which corresponds to the instant application) have been considered, one reference Austria Codex 1998/99 is not considered because it is not written in English.

### *Withdrawn Claim Rejections-35 USC § 112*

4. The previous rejection of claims 83, 84, 88 and 89 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment to the claim, and applicant's response at page 14 of the amendment filed on January 23, 2006.

***New Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 60, 61, 84 107 and 108 contain the trademark/trade name Pluronic F68. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe Poloxamer 188 and, accordingly, the identification/description is indefinite.

***Maintained Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the

reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Previous rejection of claims 67-68, 71, 73, 75, 77, 83, 85, 86, 91-101, 104 and 106 under 35 U.S.C. 102(e) as being anticipated by Bailon (U.S. Patent 6,583,272 B1, priority date July 2, 1999) is maintained. Response to applicant's argument is shown below.

Bailon teaches a conjugate of erythropoietin (EPO) with poly(ethylene glycol) (PEG) and a pharmaceutical composition comprising therapeutically effective amount of the conjugate for administering to patients (column 3, lines 23-46), wherein the conjugate comprises an EPO such as human EPO and analogs having at least one free amino group and having in vivo biological activity. The EPO conjugate can be represented by formula (I), P-[NHCO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR]$_n$ , wherein R is lower alkyl, x is 2 or 3, m is 450-900, n is 1-3, n and m are such that the molecular weight of the conjugate minus the EPO is from 20 to 100 kDa (column 1, line 64-column 3, line 6; column 3, line 48-column 4, line 31) and the EPO including both naturally or recombinantly produced human erythropoietin having the amino acid sequence of SEQ ID NO:1 or 2 can be modified as analogs having 1-6 additional glycosylation sites or a rearrangement of at least one site for glycosylation, for example, the conjugate such as mono-PEG-EPO or di-PEG-EPO is prepared in a phosphate buffer, pH 7.5 with a 30 kDa methoxy PEG-SBA reagent (Examples 2, 5), and a pegylated EPO (10-400 μg/ml, Table 3; 0.6-1.2 mg/ml, Example 6) is formulated in a sulfate-containing buffer at pH 6.2, e.g., 10 mM phosphate, 140 mM sulfate, pH 6.2; 10 mM (corresponding to 1.38 mg/ml) phosphate, 40 mM (corresponding to 5.67 mg/ml) sulfate, 4% mannitol, pH 6.2; 50 mM arginine, 100 mM sulfate, pH 6.2 and these pegylated EPO in various formulations are stable at room temperature (Fig. 4; Example 8, Table 3; claims 67, 68, 71, 73, 75, 77, 83, 85, 86, 91-101, 104 and 106).

*Response to Arguments*

Applicants indicate the Declaration of Dr. Papadimitriou under 37 CFR1.132 has been submitted on February 5, 2004, and in the Declaration, Dr. Papadimitriou averred that he is the sole inventor of formulations A-I presented in Example 8, Table 3 of U.S. Patent 6,583,272 by Bailon; Applicants also indicate that the introductory paragraphs of Section 715.01 and the paragraph entitled "Derivation" of section 715.01(c) in MPEP as well as the cases (i.e., In re Mathews, 161 USPQ 176 (CCPA 1969); and In re Facius, 161 USPQ 294, 300-301) cited therein support the propriety of the Papadimitriou Declaration; and with respect to MPEP Section 716.10, the Board of Appeals and the CCPA also agree with applicant's position that joint inventorship of applications is not required for use of a Rule 1.132 Declaration to establish prior invention. For example, the In re Cloke, 2002 WL 1821684 (Bd. Pat. App. & Interf., 2002) (Appeal No. 200-0379). Therefore, the PTO's assertion that the Papadimitriou Rule 132 Declaration is insufficient to overcome the pending 102(e) rejection because there is no common inventor between the Bailon '272 patent and the instant application is legally incorrect, and the rejection should be withdrawn (pages 15-18 of the response).

Applicants' response has been fully considered. Regarding the joint inventorship of applications is not required for use of Rule 1.132, the arguments are found persuasive. However, according to the paragraph entitled "Derivation" of section 715.01(c) of MPEP, which states that

> When the unclaimed subject matter of a patent, application publication, or other publication is applicant's own invention, a rejection>, which is not a statutory bar,< on that patent or publication may be removed by submission of evidence establishing the fact that the patentee, applicant of the published application, or author derived his or her knowledge of the relevant subject matter from applicant. Moreover applicant must further show that he or she made the invention upon which the relevant disclosure in the patent, application publication, or other publication is based.

This statement indicates it requires submission of evidence establishing the fact that the patentee derived his or her knowledge of the relevant subject matter from applicant, and applicant must further show that he or she made the invention upon which the relevant disclosure in the patent, is based. However, in the Declaration, Dr. Papadimitriou merely stated that he is the source of the pharmaceutical compositions comprising the peg-EPO disclosed in the Bailon '272 patent and is the sole inventor of these compositions without providing supported documents that indicate the claimed composition comprising P-[NHCO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR]$_n$ was first disclosed to the patentee by the inventor of instant application, nor has shown the claimed composition comprising P-[NHCO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR]$_n$ was invented prior to the filing date of the '272 patent, while the P-[NHCO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR]$_n$ (i.e., n=1) is the claimed invention in the patent '272, and Bailon is the sole inventor of the patent '272. Therefore, the Papadimitriou's Declaration is insufficient to overcome the pending 102(e) rejection.

***New Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 72, 74, 76, 84, 87-89, 102, 103, 105, 107 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailon (U.S. Patent No. 6,583,272, effective filing date, July 2, 1999) in view of Sato (WO 00/51629, published on September 8, 2000) based on

the English Equivalent patent (U. S. Patent 6,908,610) as evidenced by Papadimitriou (US 2002/0037841).

Bailon teaches a conjugate comprising an erythropoietin (EPO) glycoprotein having at least one free amino group and having the in vivo biological activity and a poly(ethylene glycol) (peg) group; and a pharmaceutical composition comprising the conjugate and a pharmaceutically acceptable carrier (column 2, line 56-column 3, line 6; column 3, lines 41-47), wherein the peg-EPO is prepared in various formulations (Table 3; Example 8), e.g., formulation C containing 10 or 100 μg/ml peg-EPO, 10 mM (corresponding to 1.38 mg/ml) phosphate, 140 mM sodium sulfate, pH 6.2; formulation D containing 10 or 100 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate (corresponding to 5.68 mg/ml), pH 6.2; formulation E containing 50 or 400 μg/ml peg-EPO, 10 mM phosphate, 100 mM sodium chloride, pH 7.0; formulation G containing 400 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate, 3% mannitol (w/v), pH 6.2. Although the concentration of arginine (e.g., 50 mM) or sodium sulfate (40 mM or 120 mM) in some conditions in the Bailon reference is different form those cited in the claimed composition (e.g., arginine, 40 mM; sodium sulfate, 30 mM), the concentrations of these components in the Bailon reference can be optimized through routine experimentation (See MPEP 2144.05 II A). However, Bailon does not disclose the use of methionine as an antioxidant and poloxamer 188 as a non-ionic surfactant in the pharmaceutical composition.

Sato teaches a stabilized composition containing a physiologically active protein having a methionine residue, further containing methionine and one or more other amino acids, where the addition of methionine inhibits the protein from producing a variant oxidized at methionine residue, and wherein the physiologically active protein can be granulocyte colony-stimulating

factors (G-CSF), EPO or PTH (column 3, lines 16-20, 36-40; column 8, lines 14-41), the amount of methionine is about 0.001-5 mg/ml (where 1.49 mg/ml corresponds to 10 mM), and the composition contains buffer such as phosphate and citrate (column 5, lines 12-20; column 6, lines 47-54), and a non-ionic surfactant such as polysorbate 20 (column 2, lines 41-46; Table 1, where 0.1 mg/ml corresponds to 0.01% polysorbate 20).

At the invention was made, it would have been obvious that one of ordinary skill in the art is motivated to add methionine as taught by Sato to the pharmaceutical composition comprising EPO-PEG conjugate as taught by Bailon (claims 87-89, 102, 103 and 105) because addition of methionine to the pharmaceutical composition comprising EPO conjugate would increase the stability of EPO conjugate in the pharmaceutical composition. Furthermore, one of ordinary skill in the art is motivated to add a non-ionic surfactant such as polysorbate 20 as taught by Sato or pluronic F68 as evidenced by Papadimitriou (US 2002/0037841; paragraph [0046]) to a pharmaceutical composition as taught by Bailon (claims 72, 74, 76, 84, 107 and 108) because either pluronic F68 (trademark name for poloxamer 188) or polysorbate 20 can be used as a non-ionic surfactant (Papadimitriou, paragraph [0046]). Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

***Conclusion***

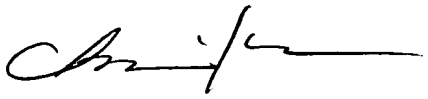
8. Claims 60, 61, 67-68, 71-77, 83-89 and 91-108 are rejected. It appears that claims 24, 25, 27-34, 38-42, 51-55, 59 and 90 are free of art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner



CHIH-MIN KAM
PATENT EXAMINER

CMK
April 10, 2006